EXHIBIT 1

PDR® 48 EDITION 1994

PHYSICIANS' DESK REFERENCE®

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Ciprofloxacin does not cross-react with other antimicrobial agents such as beta-lactams or aminoglycosides; therefore, organisms resistant to these drugs may be susceptible to ciprofloxacin.

Clinical Studies:
Following therapy with CILOXAN Ophthalmic Solution, 76% of the patients with corneal ulcers and positive bacterial cultures were clinically cured and complete re-epithelialization occurred in about 92% of the ulcers.
In 3 and 7 day multicenter clinical trials, 52% of the patients with conjunctivitis and positive conjunctival cultures were clinically cured and 70–80% had all causative pathogens eradicated by the end of treatment.

INDICATIONS AND USAGE

CILOXAN Ophthalmic Solution is indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below:

Corneal Ulcers:	*Pseudomonas aeruginosa*
	*Serratia marcescens**
	Staphylococcus aureus
	Staphylococcus epidermidis
	Streptococcus pneumoniae
	Streptococcus (Viridans Group)*
Conjunctivitis:	*Staphylococcus aureus*
	Staphylococcus epidermidis
	*Streptococcus pneumoniae**

*Efficacy for this organism was studied in fewer than 10 infections.

CONTRAINDICATIONS

A history of hypersensitivity to ciprofloxacin or any other component of the medication is a contraindication to its use. A history of hypersensitivity to other quinolones may also contraindicate the use of ciprofloxacin.

WARNINGS

NOT FOR INJECTION INTO THE EYE.
Serious and occasionally fatal hypersensitivity (anaphylactic) reactions, some following the first dose, have been reported in patients receiving systemic quinolone therapy. Some reactions were accompanied by cardiovascular collapse, loss of consciousness, tingling, pharyngeal or facial edema, dyspnea, urticaria, and itching. Only a few patients had a history of hypersensitivity reactions. Serious anaphylactic reactions require immediate emergency treatment with epinephrine and other resuscitation measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines and airway management, as clinically indicated.

PRECAUTIONS

General: As with other antibacterial preparations, prolonged use of ciprofloxacin may result in overgrowth of non-susceptible organisms, including fungi. If superinfection occurs, appropriate therapy should be initiated. Whenever clinical judgment dictates, the patient should be examined with the aid of magnification, such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
Ciprofloxacin should be discontinued at the first appearance of a skin rash or any other sign of hypersensitivity reaction.
In clinical studies of patients with bacterial corneal ulcer, a white crystalline precipitate located in the superficial portion of the corneal defect was observed in 35 (16.6%) of 210 patients. The onset of the precipitate was within 24 hours to 7 days after starting therapy. In one patient, the precipitate was immediately irrigated out upon its appearance. In 17 patients, resolution of the precipitate was seen in 1 to 8 days (seven within the first 24–72 hours); in five patients, resolution was noted in 10–13 days. In nine patients, exact resolution days were unavailable; however, at follow-up examinations, 18–44 days after onset of the event, complete resolution of the precipitate was noted. In three patients, outcome information was unavailable. The precipitate did not preclude continued use of ciprofloxacin, nor did it adversely affect the clinical course of the ulcer or visual outcome. (SEE ADVERSE REACTIONS).
Drug Interactions: Specific drug interaction studies have not been conducted with ophthalmic ciprofloxacin. However, the systemic administration of some quinolones has been shown to elevate plasma concentrations of theophylline, interfere with the metabolism of caffeine, enhance the effects of the oral anticoagulant, warfarin, and its derivatives and have been associated with transient elevations in serum creatinine in patients receiving cyclosporine concomitantly.
Carcinogenesis, Mutagenesis, Impairment of Fertility: Eight *in vitro* mutagenicity tests have been conducted with ciprofloxacin and the test results are listed below:
Salmonella/Microsome Test (Negative)
E. coli DNA Repair Assay (Negative)
Mouse Lymphoma Cell Forward Mutation Assay (Positive)
Chinese Hamster V_{79} Cell HGPRT Test (Negative)
Syrian Hamster Embryo Cell Transformation Assay (Negative)
Saccharomyces cerevisiae Point Mutation Assay (Negative)
Saccharomyces cerevisiae Mitotic Crossover and Gene Conversion Assay (Negative)
Rat Hepatocyte DNA Repair Assay (Positive)
Thus, two of the eight tests were positive, but the results of the following three *in vivo* test systems gave negative results:
Rat Hepatocyte DNA Repair Assay
Micronucleus Test (Mice)
Dominant Lethal Test (Mice)
Long term carcinogenicity studies in mice and rats have been completed. After daily oral dosing for up to two years, there is no evidence that ciprofloxacin had any carcinogenic or tumorigenic effects in these species.
Pregnancy—Pregnancy Category C: Reproduction studies have been performed in rats and mice at doses up to six times the usual daily human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to ciprofloxacin. In rabbits, as with most antimicrobial agents, ciprofloxacin (30 and 100 mg/kg orally) produced gastrointestinal disturbances resulting in maternal weight loss and an increased incidence of abortion. No teratogenicity was observed at either dose. After intravenous administration, at doses up to 20 mg/kg, no maternal toxicity was produced and no embryotoxicity or teratogenicity was observed. There are no adequate and well controlled studies in pregnant women. CILOXAN Ophthalmic Solution should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers: It is not known whether topically applied ciprofloxacin is excreted in human milk; however, it is known that orally administered ciprofloxacin is excreted in the milk of lactating rats and oral ciprofloxacin has been reported in human breast milk after a single 500 mg dose. Caution should be exercised when CILOXAN Ophthalmic Solution is administered to a nursing mother.
Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.
Although ciprofloxacin and other quinolones cause arthropathy in immature animals after oral administration, topical ocular administration of ciprofloxacin to immature animals did not cause any arthropathy and there is no evidence that the ophthalmic dosage form has any effect on the weight bearing joints.

ADVERSE REACTIONS

The most frequently reported drug related adverse reaction was local burning or discomfort. In corneal ulcer studies with frequent administration of the drug, white crystalline precipitates were seen in approximately 17% of patients (SEE PRECAUTIONS). Other reactions occurring in less than 10% of patients included lid margin crusting, crystals/scales, foreign body sensation, itching, conjunctival hyperemia and a bad taste following instillation. Additional events occuring in less than 1% of patients included corneal staining, keratopathy/keratitis, allergic reactions, lid edema, tearing, photophobia, corneal infiltrates, nausea and decreased vision.

OVERDOSAGE

A topical overdose of CILOXAN Ophthalmic Solution may be flushed from the eye(s) with warm tap water.

DOSAGE AND ADMINISTRATION

The recommended dosage regimen for the treatment of **corneal ulcers** is: Two drops into the affected eye every 15 minutes for the first six hours and then two drops into the affected eye every 30 minutes for the remainder of the first day. On the second day, instill two drops in the affected eye hourly. On the third through the fourteenth day, place two drops in the affected eye every four hours. Treatment may be continued after 14 days if corneal re-epithelialization has not occurred.
The recommended dosage regimen for the treatment of **bacterial conjunctivitis** is: One or two drops instilled into the conjunctival sac(s) every two hours while awake for two days and one or two drops every four hours while awake for the next five days.

HOW SUPPLIED

As a sterile ophthalmic solution: 2.5 mL and 5 mL in plastic DROP-TAINER® dispensers.
2.5 mL—NDC 0065-0656-25
5 mL —NDC 0065-0656-05

STORAGE

Store at 2° to 30°C (36° to 86°F). Protect from light.

ANIMAL PHARMACOLOGY

Ciprofloxacin and related drugs have been shown to cause arthropathy in immature animals of most species tested following oral administration. However, a one-month topical ocular study using immature Beagle dogs did not demonstrate any articular lesions.

CAUTION

Federal (USA) law prohibits dispensing without prescription.
U.S. Patent No. 4,670,444

EYE-STREAM® **OTC**
Sterile Eye Irrigating Solution

EYE-STREAM® is a sterile and stable irrigating solution that is specially designed and packaged for use in the eye(s). Formulated as a buffered salt solution, it closely approximates normal human tear fluid.

INGREDIENTS

Each mL contains: **Tonicity Agents:** Sodium Chloride 0.64%, Potassium Chloride 0.075%, Calcium Chloride Dihydrate 0.048%, Magnesium Chloride Hexahydrate 0.03%. **Buffering Agents:** Sodium Acetate Trihydrate 0.39%, Sodium Citrate Dihydrate 0.17%. **pH Adjusters:** Sodium Hydroxide and/or Hydrochloric Acid. **Preservative:** Benzalkonium Chloride 0.013%. **Purified Water.** The pH of the solution is in the physiologic range.

INDICATIONS

FDA APPROVED USES
For irrigating the eye to help relieve irritation, discomfort and burning by removing loose foreign material, air pollutants (smog or pollen), or chlorinated water.

WARNINGS

If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists, consult a doctor. Obtain immediate medical treatment for all open wounds in or near the eyes. If solution changes color or becomes cloudy, do not use. To avoid contamination, do not touch tip of container to any surface. Replace cap after using. Keep this and all drugs out of the reach of children. In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately. Not to be used as a saline solution for rinsing and soaking soft contact lenses. **NOT FOR INJECTION OR INTRAOCULAR SURGERY.**

DIRECTIONS

Flush the affected eye as needed, controlling the rate of flow of solution by pressure on the bottle. Please read this carton carefully and keep for future reference.

HOW SUPPLIED

In 1 fluid ounce and 4 fluid ounce plastic squeeze bottles.
1 fl. oz: NDC 0065-0530-01
4 fl. oz.: NDC 0065-0530-04

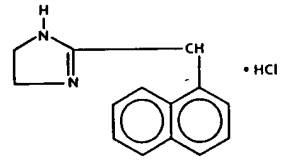
STORAGE

Store at 8°–27°C (46°–80°F).

NAPHCON-A® ℞
(naphazoline hydrochloride and pheniramine maleate)
Sterile Ophthalmic Solution

DESCRIPTION

NAPHCON-A® (naphazoline hydrochloride, pheniramine maleate) is a combination of an antihistamine and a decongestant prepared as a sterile topical ophthalmic solution. The active ingredients are represented by the chemical structures:



Established name:
Naphazoline Hydrochloride
Chemical name:
1*H*-Imidazole, 4, 5-dihydro- 2-(1- naphthalenylmethyl)-, monohydrochloride.

Established name:
Pheniramine Maleate
Chemical name:
N,N-Dimethyl -γ -phenyl -2- pyridine-propanamine, (Z)-Butenedioic acid.

Each mL contains: Active: Naphazoline Hydrochloride 0.025%, Pheniramine Maleate 0.3%. Preservative: Benzal-

Continued on next page

Alcon Laboratories—Cont.

konium Chloride 0.01%. Inactive: Boric Acid, Sodium Borate, Edetate Disodium, Sodium Chloride, Sodium Hydroxide and/or Hydrochloric Acid (to adjust pH), and Purified Water.

CLINICAL PHARMACOLOGY

NAPHCON-A® combines the effects of the antihistamine, pheniramine maleate, and the decongestant, naphazoline.

INDICATIONS AND USAGE: Based on a review of a related combination of drugs by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows: "Possibly" effective: For relief of ocular irritation and/or congestion or for the treatment of allergic or inflammatory ocular conditions. Final classification of the less-than-effective indication requires further investigation.

CONTRAINDICATIONS

Hypersensitivity to one or more of the components of this preparation.
Do not use in the presence of narrow angle glaucoma or in patients predisposed to narrow angle glaucoma.

WARNINGS

Patients under MAO inhibitors may experience a severe hypertensive crisis if given a sympathomimetic drug such as Naphazoline HCl. Use in infants and children may result in CNS depression leading to coma and marked reduction in body temperature.

PRECAUTIONS

General
For topical eye use only—not for injection. This preparation should be used with caution in patients with severe cardiovascular disease including cardiac arrhythmias, patients with poorly controlled hypertension, patients with diabetes, especially those with a tendency toward diabetic ketoacidosis.
Information For Patients: To prevent contaminating the dropper tip and solution, care should be taken not to touch the eyelids or surrounding area with the dropper tip of the bottle.
Carcinogenesis, Mutagenesis, Impairment of Fertility: There have been no long-term studies done using naphazoline hydrochloride and/or pheniramine maleate in animals to evaluate carcinogenic potential.
Pregnancy: Pregnancy Category C. Animal reproduction studies have not been conducted with naphazoline hydrochloride and/or pheniramine maleate. It is also not known whether naphazoline hydrochloride and/or pheniramine maleate can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. NAPHCON-A® Ophthalmic Solution should be given to a pregnant woman only if clearly needed.
Nursing Mothers: It is not known whether these drugs are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when NAPHCON-A Ophthalmic Solution is administered to a nursing woman.

ADVERSE REACTIONS

The following adverse reactions may occur: Pupillary dilation, increase in intraocular pressure, systemic effects due to absorption (i.e., hypertension, cardiac irregularities, hyperglycemia). Drowsiness may be experienced by some patients.

DOSAGE AND ADMINISTRATION

One or two drops instilled in each eye every 3 to 4 hours or less frequently, as required to relieve symptoms.

HOW SUPPLIED

In 15mL plastic DROP-TAINER® Dispenser.
NDC 0065-0080-15

STORAGE

Store at 2°-27°C (36°-80°F). Keep bottle tightly closed when not in use. Protect from light and excessive heat.

CAUTION

Federal (USA) law prohibits dispensing without prescription.

TEARS NATURALE® II OTC
Lubricant Eye Drops
TEARS NATURALE FREE®
Lubricant Eye Drops

DESCRIPTION

TEARS NATURALE II is the only lubricant eye drop preserved with safe, nonsensitizing POLYQUAD 0.001%. *In vitro* studies have shown that POLYQUAD substantially avoids the damaging effects of epithelial cell toxicity possible with other tear substitute preservatives and allows epithelial cell growth. POLYQUAD has been shown to be 99% reaction-free in normal subjects and 97% reaction-free in subjects known to be preservative sensitive. TEARS NATURALE FREE is a preservative-free version of TEARS NATURALE II.
With their unique mucin like polymeric formulation, and with their natural pH, low viscosity, and isotonicity, TEARS NATURALE II and TEARS NATURALE FREE provide dry eye patients with comfort and prompt relief of dry eye symptoms.
Sterile-For Topical Eye Use Only

INGREDIENTS

TEARS NATURALE II: each mL contains:
Active: DUASORB®, a water soluble polymeric system containing Dextran 70 0.1% and Hydroxypropyl Methylcellulose 2910 0.3%.
Preservative: POLYQUAD®* (Polyquaternium-1) 0.001%.
Inactive: Sodium Borate, Potassium Chloride, Sodium Chloride, Purified Water. May contain Hydrochloric Acid and/or Sodium Hydroxide to adjust pH.
TEARS NATURALE FREE: each mL contains:
Active: DUASORB, a water soluble polymeric system containing Dextran 70 0.1% and Hydroxypropyl Methylcellulose 2910 0.3%.
Inactive: Sodium Borate, Potassium Chloride, Sodium Chloride, Purified Water. May contain Hydrochloric Acid and/or Sodium Hydroxide to adjust pH.

INDICATIONS

For the temporary relief of burning and irritation due to dryness of the eye and for use as a protectant against further irritation. For temporary relief of discomfort due to minor irritations of the eye or to exposure to wind or sun.

WARNINGS

Remove contact lenses before using.
If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists for more than 72 hours, discontinue use and consult a doctor.
If solution changes color or becomes cloudy, do not use.
To avoid contamination, do not touch tip of container to any surface. TEARS NATURALE II: Replace cap after using. TEARS NATURALE FREE: Do not reuse. Once opened, discard. Keep this and all drugs out of the reach of children. In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.

DIRECTIONS

TEARS NATURALE II: Instill 1 or 2 drops in the affected eye(s) as needed. TEARS NATURALE FREE: Completely twist off tab: do not pull. Instill 1 or 2 drops in the affected eye(s) as needed.

HOW SUPPLIED

TEARS NATURALE II Lubricant Eye Drops are supplied in 15 mL and 30 mL plastic DROP-TAINER® bottles.
15 mL NDC 0065-0418-15
30 mL NDC 0065-0418-32
TEARS NATURALE FREE Lubricant Eye Drops are supplied in boxes of 32 0.02 fl. oz. single-use containers.
NDC 0065-0416-32

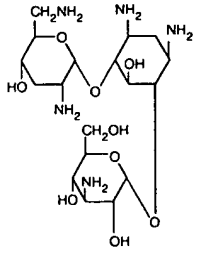
STORAGE

Store at room temperature.

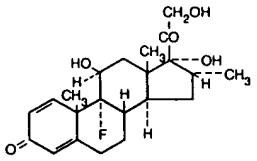
TOBRADEX® Rx
(Tobramycin and Dexamethasone)
Sterile Ophthalmic Suspension and Ointment

DESCRIPTION

TOBRADEX® (Tobramycin and Dexamethasone) Ophthalmic Suspension and Ointment are sterile, multiple dose antibiotic and steroid combinations for topical ophthalmic use. The chemical structures for tobramycin and dexamethasone are presented below:



Tobramycin
Empirical Formula: $C_{18}H_{37}N_5O_9$
Chemical name:
O-3-Amino-3-deoxy-α-D-glucopyranosyl-(1→4)-*O*-[2,6-diamino-2,3,6-trideoxy-α-D-*ribo*-hexopyranosy 2-deoxy-L-streptamine



Dexamethasone
Empirical Formula: $C_{22}H_{29}FO_5$
Chemical Name:
9-Fluoro-11β,17,21-trihydroxy-16α-methylpregna-1 3,20-dione

Each mL of TOBRADEX® Suspension contain: Tobramycin 0.3% (3 mg) and Dexamethasone 0.1 Preservative: Benzalkonium Chloride 0.01%. Tyloxapol, Edetate Disodium, Sodium Chloride, ethyl Cellulose, Sodium Sulfate, Sulfuric Acid a dium Hydroxide (to adjust pH) and Purified Wat Each gram of TOBRADEX® Ointment contain Tobramycin 0.3% (3 mg) and Dexamethasone 0.1 Preservative: Chlorobutanol 0.5%. Inactive: Miner White Petrolatum.

CLINCIAL PHARMACOLOGY

Corticoids suppress the inflammatory response to of agents and they probably delay or slow healing. ticoids may inhibit the body's defense mechanis infection, a concomitant antimicrobial drug ma when this inhibition is considered to be clinically si Dexamethasone is a potent corticoid.
The antibiotic component in the combination (tobr included to provide action against susceptible org *vitro* studies have demonstrated that tobramycin against susceptible strains of the following microo Staphylococci, including *S. aureus* and *S. epidermi* lase-positive and coagulase-negative), including resistant strains.
Streptococci, including some of the Group A beta species, some nonhemolytic species, and some *Str pneumoniae.*
Pseudomonas aeruginosa, Escherichia coli, Klebsi moniae, Enterobacter aerogenes, Proteus mirab ganella morganii, most *Proteus vulgaris* strains, *l lus influenzae* and *H. aegyptius, Moraxella lacu Acinetobacter calcoaceticus* and some *Neisseria* sp Bacterial susceptibility studies demonstrate tha cases microorganisms resistant to gentamicin re ceptible to tobramycin. A significant bacterial resistant to tobramycin has not yet emerged; howe rial resistance may develop upon prolonged use.
No data are available on the extent of systemic from TOBRADEX® Ophthalmic Suspension or however, it is known that some systemic absorpti cur with ocularly applied drugs. If the maximum c BRADEX Ophthalmic Suspension is given for t hours (two drops in each eye every 2 hours) and systemic absorption occurs, which is highly unl daily dose of dexamethasone would be 2.4 mg. physiologic replacement dose is 0.75 mg dail BRADEX Ophthalmic Suspension is given after t hours as two drops in each eye every 4 hours, th tered dose of dexamethasone would be 1.2 mg dail ministered dose for TOBRADEX Ophthalmic Oi both eyes four times daily would be 0.4 mg of dexa daily.

INDICATIONS AND USAGE

TOBRADEX® Ophthalmic Suspension and Oin indicated for steroid-responsive inflammatory oc tions for which a corticosteroid is indicated and wh ficial bacterial ocular infection or a risk of bacte infection exists.
Ocular steroids are indicated in inflammatory co the palpebral and bulbar conjunctiva, cornea an segment of the globe where the inherent risk of ste certain infective conjunctivitides is accepted to ob inution in edema and inflammation. They are als in chronic anterior uveitis and corneal injury fron radiation or thermal burns, or penetration of fore The use of a combination drug with an anti-infect nent is indicated where the risk of superficial oc tion is high or where there is an expectation that dangerous numbers of bacteria will be present i The particular anti-infective drug in this produ against the following common bacterial eye patl

Wyeth-Ayerst Laboratories—Cont.

COLLYRIUM for FRESH EYES OTC

[*ko-lir'e-um*]
A neutral borate solution
EYE WASH

DESCRIPTION

Soothing Collyrium Eye Wash for Fresh Eyes is specially formulated to soothe, refresh, and cleanse irritated eyes. Collyrium Eye Wash is a neutral borate solution that contains boric acid, sodium borate, benzalkonium chloride as a preservative, and water.

INDICATIONS

Patients are advised of the following. Use Collyrium Eye Wash to cleanse the eye, loosen foreign material, air pollutants or chlorinated water.

RECOMMENDED USES

Home—For emergency flushing of foreign bodies or whenever a soothing eye rinse is necessary.
Hospitals, dispensaries and clinics—For emergency flushing of chemicals or foreign bodies from the eye.

DOSAGE AND ADMINISTRATION

Patients are advised of the following. Remove the eyecup from blister. Puncture bottle by twisting threaded eyecup fully down onto bottle; then remove it from the bottle. Rinse eyecup with clean water immediately before and after each use. Avoid contamination of rim and interior surfaces of eyecup. Fill eyecup one-half full with Collyrium Eye Wash. Apply cup tightly to the affected eye to prevent the escape of the liquid and tilt head backward. Open eyelid wide and rotate eyeball to thoroughly wash eye. Rinse cup with clean water after use and recap by twisting threaded eyecup on the bottle for storage.

WARNINGS

Patients are advised of the following. Do not use if solution changes color or becomes cloudy, or with a wetting solution for contact lenses or other eye care products containing polyvinyl alcohol. This product contains benzalkonium chloride as a preservative. Do not use this product if you are sensitive to benzalkonium chloride.
To avoid contamination do not touch tip of container to any surface. Replace cap after using. If you experience eye pain, changes in vision, continued redness, irritation of the eye, or if the condition worsens or persists, consult a doctor. Obtain immediate medical treatment for all open wounds in or near the eyes.
The COLLYRIUM for FRESH EYES bottle is sealed for your protection. Prior to first use, remove cap and squeeze bottle. If bottle leaks, do not use.
Keep this and all medication out of the reach of children. Keep bottle tightly closed at Room Temperature, Approx. 77° F (25° C).

HOW SUPPLIED

Bottles of 4 FL. OZ. (118 mL) with eyecup.

COLLYRIUM FRESH™ OTC

[*ko-lir'e-um*]
Sterile Eye Drops
Lubricant ○ Redness Reliever

DESCRIPTION

Collyrium Fresh is a specially formulated sterile eye drop which can be used, up to 4 times daily, to relieve redness and discomfort due to minor eye irritations caused by dust, smoke, smog, swimming, or sun glare.
The active ingredients are tetrahydrozoline HCl (0.05%) and glycerin (1.0%). Other ingredients include benzalkonium chloride (0.01%) and edetate disodium (0.1%) as preservatives, boric acid, hydrochloric acid and sodium borate.

INDICATIONS

Patients are advised of the following. For the temporary relief of redness due to minor eye irritations or discomfort due to burning or exposure to wind or sun.

DOSAGE AND ADMINISTRATION

Patients are advised of the following. Tilt head back and squeeze 1 to 2 drops into each eye up to 4 times daily, or as directed by a physician.

WARNINGS

Patients are advised of the following. Do not use if solution changes color or becomes cloudy. Remove contact lenses before using. If you have glaucoma, do not use this product except under the advice and supervision of a physician. Overuse of this product may produce increased redness of the eye. To avoid contamination, do not touch tip of container to any surface. Replace cap after using. If you experience eye pain, changes in vision, continued redness or irritation of the eye, or if the condition worsens or persists for more than 72 hours, discontinue use and consult a physician.
Keep this and all medication out of the reach of children. The product's carton should be retained for complete product information.
Keep bottle tightly closed at Room Temperature, Approx. 77° F (25° C).

HOW SUPPLIED

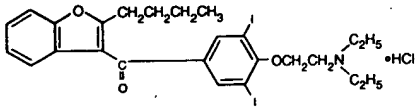
Bottles of 0.5 FL. OZ. (15 mL) with built-in eye dropper.

CORDARONE® ℞

[*kŏr'dă-rōn*]
(amiodarone HCl)
Tablets

DESCRIPTION

Cordarone is a member of a new class of antiarrhythmic drugs with predominantly Class III (Vaughan Williams' classification) effects, available for oral administration as white, scored tablets containing 200 mg of amiodarone hydrochloride. The inactive ingredients present are colloidal silicon dioxide, lactose, magnesium stearate, povidone, starch, and FD&C Red 40. Cordarone is a benzofuran derivative: 2-butyl-3-benzofuranyl 4-[2-(diethylamino)-ethoxy]-3,5-diiodophenyl ketone, hydrochloride. It is not chemically related to any other available antiarrhythmic drug.
The structural formula is as follows:



$C_{25}H_{29}I_2NO_3 \cdot HCl$ Molecular Weight: 681.8

Amiodarone HCl is a white to cream-colored crystalline powder. It is slightly soluble in water, soluble in alcohol, and freely soluble in chloroform. It contains 37.3% iodine by weight.

CLINICAL PHARMACOLOGY

ELECTROPHYSIOLOGY/MECHANISMS OF ACTION
In animals, Cordarone is effective in the prevention or suppression of experimentally induced arrhythmias. The antiarrhythmic effect of Cordarone may be due to at least two major properties: 1) a prolongation of the myocardial cell-action potential duration and refractory period and 2) noncompetitive alpha- and beta-adrenergic inhibition.
Cordarone prolongs the duration of the action potential of all cardiac fibers while causing minimal reduction of dV/dt (maximal upstroke velocity of the action potential). The refractory period is prolonged in all cardiac tissues. Cordarone increases the cardiac refractory period without influencing resting membrane potential, except in automatic cells where the slope of the prepotential is reduced, generally reducing automaticity. These electrophysiologic effects are reflected in a decreased sinus rate of 15 to 20%, increased PR and QT intervals of about 10%, the development of U-waves, and changes in T-wave contour. These changes should not require discontinuation of Cordarone as they are evidence of its pharmacological action, although Cordarone can cause marked sinus bradycardia or sinus arrest and heart block. On rare occasions, QT prolongation has been associated with worsening of arrhythmia (see "Warnings").
HEMODYNAMICS
In animal studies and after intravenous administration in man, Cordarone relaxes vascular smooth muscle, reduces peripheral vascular resistance (afterload), and slightly increases cardiac index. After oral dosing, however, Cordarone produces no significant change in left ventricular ejection fraction (LVEF), even in patients with depressed LVEF. After acute intravenous dosing in man, Cordarone may have a mild negative inotropic effect.
PHARMACOKINETICS
Following oral administration in man, Cordarone is slowly and variably absorbed. The bioavailability of Cordarone is approximately 50%, but has varied between 35 and 65% in various studies. Maximum plasma concentrations are attained 3 to 7 hours after a single dose. Despite this, the onset of action may occur in 2 to 3 days, but more commonly takes 1 to 3 weeks, even with loading doses. Plasma concentrations with chronic dosing at 100 to 600 mg/day are approximately dose proportional, with a mean 0.5 mg/L increase for each 100 mg/day. These means, however, include considerable individual variability.
Cordarone has a very large but variable volume of distribution, averaging about 60 L/kg because of extensive accumulation in various sites, especially adipose tissue and highly perfused organs, such as the liver, lung, and spleen. One major metabolite of Cordarone, desethylamiodarone, has been identified in man; it accumulates to an even greater extent in almost all tissues. The pharmacological activity of this metabolite, however, is not known. During chronic treatment, the plasma ratio of metabolite to parent compound is approximately one.
The main route of elimination is via hepatic excretion into bile, and some enterohepatic recirculation may occur. However, its kinetics in patients with hepatic insufficiency have not been elucidated. Cordarone has a very low plasma clearance with negligible renal excretion, so that it does not appear necessary to modify the dose in patients with renal failure. In patients with renal impairment, the plasma concentration of Cordarone is not elevated. Neither Cordarone nor its metabolite is dialyzable.
In patients, following discontinuation of chronic oral therapy, Cordarone has been shown to have a biphasic elimination with an initial one-half reduction of plasma levels after 2.5 to 10 days. A much slower terminal plasma-elimination phase shows a half-life of the parent compound ranging from 26 to 107 days, with a mean of approximately 53 days and most patients in the 40- to 55-day range. In the absence of a loading-dose period, steady-state plasma concentrations, on constant oral dosing, would therefore be reached between 130 and 535 days, with an average of 265 days. For the metabolite, the mean plasma-elimination half-life was approximately 61 days. These data probably reflect an initial elimination of the drug from well-perfused tissue (the 2.5- to 10-day half-life phase), followed by a terminal phase representing extremely slow elimination from poorly perfused tissue compartments such as fat.
The considerable intersubject variation in both phases of elimination, as well as uncertainty as to what compartment is critical to drug effect, requires attention to individual responses once arrhythmia control is achieved with loading doses because the correct maintenance dose is determined, in part, by the elimination rates. Daily maintenance doses of Cordarone should be based on individual patient requirements (see "Dosage and Administration").
Cordarone and its metabolite have a limited transplacental transfer of approximately 10 to 50%. The parent drug and its metabolite have been detected in breast milk.
Cordarone is highly protein-bound (approximately 96%).
Although electrophysiologic effects, such as prolongation of QTc, can be seen within hours after a parenteral dose of Cordarone, effects on abnormal rhythms are not seen before 2 to 3 days and usually require 1 to 3 weeks, even when a loading dose is used. There may be a continued increase in effect for longer periods still. There is evidence that the time to effect is shorter when a loading-dose regimen is used.
Consistent with the slow rate of elimination, antiarrhythmic effects persist for weeks or months after Cordarone is discontinued, but the time of recurrence is variable and unpredictable. In general, when the drug is resumed after recurrence of the arrhythmia, control is established relatively rapidly compared to the initial response, presumably because tissue stores were not wholly depleted at the time of recurrence.
PHARMACODYNAMICS
There is no well-established relationship of plasma concentration to effectiveness, but it does appear that concentrations much below 1 mg/L are often ineffective and that levels above 2.5 mg/L are generally not needed. Within individuals dose reductions and ensuing decreased plasma concentrations can result in loss of arrhythmia control. Plasma-concentration measurements can be used to identify patients whose levels are unusually low, and who might benefit from a dose increase, or unusually high, and who might have dosage reduction in the hope of minimizing side effects. Some observations have suggested a plasma concentration, dose, or dose/duration relationship for side effects such as pulmonary fibrosis, liver-enzyme elevations, corneal deposits and facial pigmentation, peripheral neuropathy, gastrointestinal and central nervous system effects.
MONITORING EFFECTIVENESS
Predicting the effectiveness of any antiarrhythmic agent in long-term prevention of recurrent ventricular tachycardia and ventricular fibrillation is difficult and controversial, with highly qualified investigators recommending use of ambulatory monitoring, programmed electrical stimulation with various stimulation regimens, or a combination of these, to assess response. There is no present consensus on many aspects of how best to assess effectiveness, but there is a reasonable consensus on some aspects:

1. If a patient with a history of cardiac arrest does not manifest a hemodynamically unstable arrhythmia during electrocardiographic monitoring prior to treatment, assessment of the effectiveness of Cordarone requires some provocative approach, either exercise or programmed electrical stimulation (PES).
2. Whether provocation is also needed in patients who do manifest their life-threatening arrhythmia spontaneously is not settled, but there are reasons to consider PES or other provocation in such patients. In the fraction of patients whose PES-inducible arrhythmia can be made noninducible by Cordarone (a fraction that has varied widely in various series from less than 10% to almost 40%, perhaps due to different stimulation criteria), the prognosis has been almost uniformly excellent, with very low recurrence (ventricular tachycardia or sudden death) rates. More controversial is the meaning of continued in-